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Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing

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Abstract

Tacrolimus is the mainstay immunosuppressant drug used after solid organ and hematopoietic stem cell transplantation. Individuals who express *CYP3A5* (extensive and intermediate metabolizers) generally have decreased dose-adjusted trough concentrations of tacrolimus as compared to those who are *CYP3A5* non-expressers (poor metabolizers), possibly delaying achievement of target blood concentrations. We summarize evidence from the published literature supporting this association and provide dosing recommendations for tacrolimus based on *CYP3A5* genotype when known (updates at www.pharmgkb.org).

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Conflict of Interest

All other authors declare no conflicts.

Keywords

Tacrolimus; CYP3A5; immunosuppressant; pharmacogenetics; pharmacogenomics; transplant

Introduction

Tacrolimus is a widely used immunosuppressive medication with a narrow therapeutic index and large between-patient pharmacokinetic variability, which is partly due to genetic variations in *CYP3A5*. The purpose of this guideline is to provide information relevant to the interpretation of *CYP3A5* genotype results to guide dosing of tacrolimus. Detailed guidelines for use of tacrolimus as well as analyses of cost effectiveness are not discussed. CPIC guidelines are periodically updated at <http://www.pharmgkb.org>.

Focused Literature Review

A systematic literature review focused on *CYP3A5* genotype and tacrolimus use (see Supplemental Material online) was conducted.

Gene: *CYP3A5*

Background

Enzymes in the cytochrome P450 (CYP) 3A family are responsible for the oxidative metabolism of tacrolimus. Four genes in this family have been described, but only *CYP3A4* and *CYP3A5* are thought to be relevant in adults. *CYP3A7* is only expressed in fetal liver and *CYP3A43* is of uncertain significance. There is a high degree of sequence homology between *CYP3A4* and *CYP3A5* and thus substrate overlap (1). Both first pass metabolism and systemic clearance of drugs metabolized by *CYP3A5* are susceptible to genetically determined differences in enzyme expression. Variant alleles for *CYP3A5* (*3, *6, or *7) may result in truncated mRNA with loss of expression of the functional protein in homozygotes or compound heterozygotes, or encode non-functional protein (2). The physiological function of *CYP3A5* is unclear. Whereas *CYP3A4* poor metabolizers are rare, absence of functional *CYP3A5* is the norm in many populations. This is most notable for Caucasians with 80–85% of the population being homozygous for the variant *CYP3A5**3 allele (3). It appears that retention of *CYP3A5* expression has been under some evolutionary selection pressure in populations originating close to the equator and loss of this positive selection pressure with migration away from the equator, possibly related to the benefits derived from a sodium retaining phenotype in hot climates (4).

Genetic Test Interpretation

Each named * allele is defined by the genotype at one or more specific SNPs (Supplemental Table S1). The function associated with these allelic variants is summarized in Supplemental Table S2. The assignment of the likely *CYP3A5* phenotype, based on * allele diplotypes, is summarized in Table 1. *CYP3A5* alleles have been extensively studied in groups with diverse geographical ancestries (Supplemental Table S3). One of the limitations inherent in

a genotype-only test is that rare or *de novo* variants may not be included in commercially available genotyping tests.

Available Genetic Test Options

See Supplementary material and www.PharmGKB.org for more information on commercially available clinical testing options.

Incidental findings

No clear diseases or conditions have been linked to variation in CYP3A5 unrelated to medication use.

Other considerations

Most genetic tests examine the presence of the CYP3A5 *3 allele. Less commonly observed and possibly not included, depending on the assay, are CYP3A5*6 and CYP3A5*7 alleles, which are associated with decreased CYP3A5 activity, similar to that observed for CYP3A5*3. Additional rare variants such as *2, *8, *9 may be found which are of unknown functional significance.

In this guideline, we use phenotype nomenclature consistent with other CYP enzymes (i.e. extensive metabolizer, intermediate metabolizer and poor metabolizer). Typically with other CYP enzymes, an extensive metabolizer would be classified as a “normal” metabolizer, and therefore, the drug dose would not change based on the patient’s genotype. However, in the case of CYP3A5 and tacrolimus, a CYP3A5 expresser (i.e. CYP3A5 extensive metabolizer or intermediate metabolizer) would require a higher recommended starting dose and the CYP3A5 non-expresser (i.e. poor metabolizer) would require the standard recommended starting dose. CYP3A5 expressers constitute the minority in European populations. Additional clinician education might be necessary to avoid confusion.

Drug: Tacrolimus

Background

Tacrolimus was approved in 1994 by the FDA as an antirejection medication for liver transplantation. Tacrolimus is a macrolide that binds to its cytoplasmic protein receptor, FK binding protein 12 (FKBP-12), in T-lymphocytes. This complex binds calcineurin, preventing dephosphorylation and nuclear translocation of nuclear factor of activated T-cells, ultimately inhibiting IL-2 production and T-lymphocyte activation (5). Today, tacrolimus is one of the most widely prescribed immunosuppressive medications in solid organ transplantation and is also increasingly being used in the treatment of glomerulonephritis and graft versus host disease (GVHD). Tacrolimus in clinical use is complicated by its high between-patient variability in pharmacokinetics as well as its narrow therapeutic index. This may lead to underexposure, potentially increasing the risk of rejection, or overexposure, with risk of toxicity including nephrotoxicity, hypertension, neurotoxicity, and hyperglycemia (6). As a result, current management of tacrolimus usually includes therapeutic drug monitoring (TDM) (7). Clinically, TDM is done using tacrolimus whole blood trough concentrations which have been shown to correlate with area

under the curve measurements (8, 9). Previous studies have shown a relationship between lower tacrolimus exposure and acute rejection and higher exposure and toxicities (see Supplemental Table S4). The addition of induction therapies and mycophenolate has allowed lower target trough levels, as exemplified by the Symphony study in kidney transplant, in which patients randomized to low dose tacrolimus with target levels of 3–7ng/mL had less rejection and better kidney function (10). Though TDM is helpful for adjusting subsequent doses based on blood concentrations, it provides no information for the initial dose. Individual differences in first pass metabolism (see below) may delay reaching target blood concentrations with the initial selected dose. Furthermore, although achieving target blood concentrations does not always ensure efficacy or diminish adverse events, target blood concentrations specific for organ type and time post-transplant are available in the package insert and established by consensus guidelines (7, 11).

Demethylation and hydroxylation of tacrolimus occurs by hepatic and intestinal CYP3A isoforms (CYP3A4 and CYP3A5). Tacrolimus is also a substrate for the multidrug efflux transporter P-glycoprotein (encoded by the *ABCB1* gene, previously called *MDR1*), which is expressed on various epithelial and endothelial cells and lymphocytes. First pass metabolism by CYP3A4 and CYP3A5 in the intestine and liver contributes to the poor oral bioavailability of tacrolimus which is only around 20%. Tacrolimus is cleared through hepatic metabolism by CYP3A4 and CYP3A5 with biliary excretion of metabolites.

Linking genetic variability to variability in drug-related phenotypes

Blood concentrations of tacrolimus are strongly influenced by *CYP3A5* genotype, with substantial evidence linking *CYP3A5* genotype with phenotypic variability (see Supplemental Table S4). The application of a grading system to the evidence linking genotypic to phenotypic variability indicates a high quality of evidence in the majority of cases (see Supplemental Table S4). The evidence described below and in Supplementary Table S4 provides the basis for the dosing recommendations in Table 2.

In kidney, heart and lung transplant patients, over 50 studies have found that individuals with the *CYP3A5**1/*1 or *CYP3A5**1/*3 genotype have significantly lower dose-adjusted trough concentrations of tacrolimus as compared to those with the *CYP3A5**3/*3 genotype, with *1 carriers requiring 1.5 to 2 times the dose to achieve similar blood concentration levels (see Supplemental Table S4). *CYP3A5**1/*3 is believed to explain up to 45% of the variability in tacrolimus dose (12). Due to the rarity of the *CYP3A5**6 and *CYP3A5**7 alleles in most populations (see Supplemental Table S3), their impact on tacrolimus dose-adjusted trough concentrations has only been examined in combined analyses with *CYP3A5**3 (13, 14). However, since both alleles result in a non-functional protein (13), their impact on tacrolimus clearance and dose-adjusted trough concentrations is presumed to be identical to *CYP3A5**3.

Therapeutic Recommendations

This guideline is not intended to recommend for or against *CYP3A5* genotype testing in transplant. The current evidence for utility of *CYP3A5* genotyping to guide tacrolimus dosing is limited to *CYP3A5*'s effect on tacrolimus pharmacokinetic parameters, with no

direct evidence for improved clinical immunosuppressant outcome. As a result, we are not recommending whether or not to test for *CYP3A5* genotype in transplant, but we are providing recommendations on how to use *CYP3A5* genotype information if it is known. Since it is typical clinical practice to achieve target blood concentrations as quickly as possible, we do recommend if *CYP3A5* genotype is known, to individualize initial tacrolimus treatment using *CYP3A5* genotype to guide tacrolimus dosing as outlined in Table 2. Transplant recipients with the poor metabolizer phenotype (Table 1) should receive the standard dosing of medication based on the tacrolimus package insert. Those recipients with an extensive or intermediate metabolizer phenotype will generally require an increased dose of tacrolimus to achieve therapeutic drug concentrations. We recommend a dose 1.5–2 times higher than standard dosing, but not to exceed 0.3 mg/kg/day, followed by TDM given the risk of arterial vasoconstriction, hypertension and nephrotoxicity that can occur with supratherapeutic tacrolimus concentrations (15, 16). In addition, concomitant medications, abnormal liver function or presence of clinical conditions such as diarrhea must be taken into consideration when dosing tacrolimus (see Other Considerations below).

Given the availability of TDM, genetic testing is most helpful prior to initiation of the drug in order to more rapidly achieve therapeutic drug concentrations. This was illustrated in a randomized controlled trial by Thervet *et al.* where target tacrolimus blood concentrations were achieved earlier in new kidney transplant recipients whose tacrolimus dose was chosen based on *CYP3A5* genotype versus a control group that started tacrolimus based on standard weight-based dosing. In this study, patients received induction therapy with either basiliximab or antithymocyte globulin. Extensive metabolizers in the genotyped- dosed group had an increase in tacrolimus dose to 0.3 mg/kg/day whereas the poor metabolizers had a decrease to 0.15 mg/kg/day, and the control group received 0.2 mg/kg/day. Therapeutic drug monitoring was used in both groups. At 3 days after starting treatment with tacrolimus, significantly more of the transplant recipients in the genotyping group compared to control recipients had achieved target range (43.2% versus 29.1%, respectively) (17). However, it should be noted that tacrolimus was not started until day 7 while awaiting genotyping test results, which may differ from standard treatments with a start of tacrolimus at the time of transplantation. No differences were seen in patient survival, nephrotoxicity, or acute rejection between the groups over the 3 month follow-up. With this study as the only published randomized control trial, more data are needed to understand if dosing tacrolimus by genotype will affect clinical outcomes. However, a recent meta-analysis including 21 studies evaluating the effect of *CYP3A5* polymorphism on kidney transplant recipients concluded that there is a significantly increased risk for transplant rejection for those with the *CYP3A5**1/*1 or *CYP3A5**1/*3 genotype ($p=0.04$, $OR=1.32$). Furthermore, patients with the *CYP3A5**3/*3 (non expresser) genotype exhibited a dose-adjusted trough concentrations 1.8 to 2.5 times higher than *CYP3A5* expressers during the first year after transplantation (18).

Thus at present, there is no definitive evidence to indicate that genotype-guided dosing for tacrolimus affects long term clinical outcomes. However there is strong evidence to support its effect on achieving target trough whole blood concentrations, which is routine clinical practice for most centers (see Supplemental Table S4). Besides initial dose, genotype-guided

dosing may be also useful in patients in whom achieving therapeutic blood concentrations has been difficult, where genotype may provide some additional information to discern the reason.

In liver transplant patients, the *CYP3A5* genotype of the donor liver may not be the same as the *CYP3A5* genotype of the recipient intestine. In these cases, it may be necessary to account for both the donor and recipient genotypes when determining the dose. However, studies to date have been inconclusive as to the relative influence of the donor and recipient genotypes, and whether donor liver and recipient intestinal genotypes come into play at different points post-transplant. While some studies show that the donor genotype affects dose-adjusted trough concentrations from the first week post-transplant (19, 20), others show that it does not begin to play a role until the second week or even the sixth month post-transplant (21–23). Evidence is also conflicting for recipient intestinal genotype: a few studies show that it never significantly affects tacrolimus concentrations (20, 22, 23), whereas others show its influence on concentrations is only significant up to the point at which donor genotype becomes significant (21, 24). Due to the small number of studies analyzing these cases, as well as inconsistent results, this guideline recommendation only includes kidney, heart, lung and hematopoietic stem cell transplant patients, and liver transplant patients where the donor and recipient genotypes are identical.

Pediatrics

The effect of *CYP3A5* genotype on dose-corrected tacrolimus concentration in pediatric populations has been studied in several clinical settings, including heart (25, 26) and liver transplantation (27), but most extensively following kidney transplantation (28–33). Unfortunately, available data vary in terms of study duration following transplant and inclusion of additional factors that impact the dose-exposure relationship. In general, although the dose-exposure relationship changes over time regardless of genotype, dose-corrected tacrolimus trough concentrations are 1.5- to 2-fold higher in kidney transplant patients with *CYP3A5**3/*3 genotypes compared to patients with *CYP3A5**1/*1 or *1/*3 genotypes over the first two (31) to four (29) weeks post-transplant, at 6 months (32), and throughout the first year post-transplant (28, 30, 33). However, patient age and concurrent drug therapy also contribute to variability in the tacrolimus dose-exposure relationship in children. For example, post-pubertal renal transplant patients (age >12 years) have higher dose-corrected tacrolimus concentrations compared to younger children in the first 2–3 weeks post-transplantation period (31, 34) or over the first year post-transplant (30, 33, 34), indicative of a lower dose requirement to achieve a comparable target concentration (33). Thus, for children and adolescents with at least one *CYP3A5**1 allele, a 1.5- to 2-fold increase in dose followed by TDM as recommended for adults appears appropriate.

The Supplementary Material online contains example clinical decision support (CDS) tools that can be used within electronic health records (EHRs) which assist clinicians to use genetic information to optimize drug therapy. Clinical implementation resources include cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems (Supplementary Tables S5 and S6 online), workflow diagrams

(Supplementary Figures S1 and S2 online), and example text for documentation in the EHR and point-of care alerts (Supplementary Tables S7 and S8 online).

Recommendations for Incidental Findings

Not applicable.

Other considerations

Several drugs (drug-drug interactions) are important to consider, especially nondihydropyridine calcium channel blockers and azole anti-fungals that are commonly co-administered in the transplant population. The drug interaction with the azole anti-fungals has been reported to be less profound in CYP3A5 expressers (35, 36). For additional information on tacrolimus drug interactions, see the review by van Gelder (37). Specific patient factors such as fasting or diarrhea may cause altered absorption that can affect tacrolimus concentrations. This has been extensively reviewed in an article by Staatz et al (38).

Additional genetic variants described in the literature but with unclear effects on tacrolimus metabolism due to either limited or conflicting studies include *CYP3A4**22, *POR**28, *PPAR alpha*, and *ABCB1*. A critical issue in predicting tacrolimus clearance *in vivo* is the relative contribution of CYP3A4 compared to CYP3A5 to its metabolism. Because of the complete loss of metabolic activity with the *CYP3A5**3 allele, the impact of variation in *CYP3A4* may be high in those with no CYP3A5 expression. Of note, donor *CYP3A5* genotype may play a role in pharmacodynamics. In kidney transplant recipients, the *CYP3A5* genotype, together with the donor *ABCB1* genotype may affect the susceptibility of the kidney for tacrolimus nephrotoxicity (39). While the current guideline refers to using recipient *CYP3A5* genotype to guide selection of the optimal initial dose for tacrolimus, we can expect the potential for greater predictive value in polygenic algorithms.

A further confounding factor is the influence of ethnicity. While it was initially hypothesized that individuals of African origin require high doses of tacrolimus because of expression of CYP3A5, these individuals have high dose requirement for tacrolimus, irrespective of *CYP3A5* genotype (40). This finding suggests other factors besides *CYP3A5* genotype are important in individuals of sub Saharan African descent.

Potential Benefits and Risks for the Patient

Tacrolimus dosing is routinely directed by TDM. Yet, for patients who have an existing *CYP3A5* genotyping result, *CYP3A5* genotype guided dosing can achieve initial target tacrolimus concentrations more quickly after transplantation even when TDM based titration is used (17). Faster achievement of target concentrations could potentially reduce the risk of graft-rejection due to under-exposure and toxicity due to over-exposure. However, prospective clinical trials are needed to assess if *CYP3A5* genotype guided dosing improves these outcomes.

CYP3A5 genotyping cannot replace therapeutic drug monitoring, as other factors (i.e. demographic factors, drug-drug interactions, genetic variation affecting tacrolimus

pharmacodynamics) also influence tacrolimus dose requirements. As with any genetic test a possible risk is the misreporting or misinterpretation of genotype test results. An error in genotyping could result in an increase in tacrolimus dose and subsequently over-exposure. However, anticipated effects are limited due to stringent TDM.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

Dose alterations based on *CYP3A5* genotype may result in faster achievement of target tacrolimus concentrations with fewer dose adjustments (17). In addition, several clinical caveats apply: 1) clinical factors (e.g., age, concomitant drugs) affect tacrolimus concentrations; 2) variants in genes other than *CYP3A5* may affect tacrolimus pharmacokinetics and therefore overall exposure; 3) the relationship between tacrolimus concentration and efficacy and toxicity varies among individuals (pharmacodynamic variability); 4) the genetic determinants of tacrolimus efficacy and toxicity (pharmacodynamics) are not defined; 5) altering initial tacrolimus dosing based on *CYP3A5* genotype has not been shown to improve efficacy or reduce toxicity; and 6) monitoring of tacrolimus blood concentration remains indicated during treatment. With the expansion of our knowledge base, further refinement of the genotype-based dosing recommendations may be required.

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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W.S. and D.W. have a patent pending for a combined *CYP3A4/5* genotype panel.

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Table 1Assignment of likely metabolism phenotypes based on *CYP3A5* diplotypes

Likely phenotype	Genotypes	Examples of diplotypes*
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	*1/*1
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one non-functional allele	*1/*3, *1/*6, *1/*7
Poor metabolizer (CYP3A5 non-expresser)	An individual carrying two non-functional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7

* Additional rare variants such as *CYP3A5**2, *8, and *9 may be found which are of unknown functional significance. However, if a copy of *1 is present, expected phenotype would be intermediate metabolizer.

Table 2Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

<i>CYP3A5</i> phenotype ^a	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations ^b	Classification of Recommendations ^d
Extensive Metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5 to 2 times recommended starting dose ^c . Total starting dose should not exceed 0.3mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate Metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5 to 2 times recommended starting dose ^a . Total starting dose should not exceed 0.3mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor Metabolizer (CYP3A5 non-expresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

^aTypically with other CYP enzymes, an extensive metabolizer would be classified as a "normal" metabolizer, and therefore, the drug dose would not change based on the patient's genotype. However, in the case of CYP3A5 and tacrolimus, a CYP3A5 expresser (i.e. CYP3A5 extensive metabolizer or intermediate metabolizer) would require a higher recommended starting dose and the CYP3A5 non-expresser (i.e. poor metabolizer) would require the standard recommended starting dose.

^bThis recommendation includes the use of tacrolimus in kidney, heart, lung and hematopoietic stem cell transplant patients, and liver transplant patients where the donor and recipient genotypes are identical.

^cFurther dose adjustments or selection of alternative therapy may be necessary due to other clinical factors (e.g., medication interactions, or hepatic function)

^dRating scheme is described in Supplementary Data online.